IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	Civil Action No. 05-356-SLR
	)	(consolidated)
	)	
	)	**REDACTED PUBLIC**
	)	**VERSION**

PLAINTIFFS' REPLY MEMORANDUM IN SUPPORT OF MOTION FOR PARTIAL SUMMARY JUDGMENT REGARDING ANTICIPATION UNDER 35 U.S.C. § 102

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Plaintiffs, Janssen Pharmaceutica N.V., Janssen, L.P. and Synaptech, Inc. (collectively, "Plaintiffs") submit this Reply in support of their Motion for Partial Summary Judgment Regarding Anticipation Under 35 U.S.C. § 102. Defendants' Opposition fails to demonstrate that denial of Plaintiffs' Motion is warranted.

I. PRELIMINARY STATEMENT

Defendants' anticipation defense fails for two independent reasons. First, Defendants rely on an implausible semantic argument that seeks to interpret the Bhasker reference in a way that contradicts its plain meaning. Far from disclosing each element of the asserted claims of the '318 Patent, Bhasker does not teach or suggest anything about Alzheimer's disease except to the extent it states that progressive dementias are untreatable. Moreover, it does not meaningfully discuss the properties of galantamine or suggest that compound as a treatment for any form of progressive dementia, let alone as a specific treatment for Alzheimer's disease itself. Virtually conceding their inability to deal with Bhasker as written, Defendants attempt to rewrite and expand Bhasker through the guise expert interpretation.

Second, Defendants misapply the doctrine of inherent anticipation by claiming that elements missing from the Bhasker reference may be supplied by the alleged knowledge of one skilled in the art. This approach runs afoul of the settled rule that anticipation can only be proved by showing (in clear and convincing fashion) that each and every element of the invention is present, whether expressly or inherently, in a single piece of prior art. Hence, while extrinsic evidence may be used to show what is *necessarily present* in the reference, it cannot be used, as Defendants would use it, to fill gaps and expand the teachings of the reference. Defendants' overt attempt to make the Bhasker reference anticipating by combining it with a vast array of purported "knowledge of one of ordinary skill" (*e.g.*, Defs.' Opp. at 16-17) is simply an

inadequate obviousness attack masquerading as anticipation. Settled law forbids precisely what Defendants attempt here.

Either flaw alone fatally undermines Defendants' Opposition. Taken together, they show that Defendants cannot establish with the required convincing clarity that Bhasker discloses galantamine as a treatment for Alzheimer's disease, thus precluding a finding of anticipation. Plaintiffs' Motion should be granted.

II. ARGUMENT

A. Defendants' Failure To Show They Can Meet The Clear And Convincing Evidentiary Standard Of Patent Invalidity Is Fatal To Their Claim.

In their opposition, Defendants make the remarkable assertion that "for purposes of this motion, the threshold issue is not what [they] can or cannot prove." Defs.' Opp. at 11. To the contrary, the issue on summary judgment is precisely what the Defendants can or cannot prove. In asserting anticipation, Defendants bear the ultimate burden to prove by clear and convincing evidence that the '318 Patent is invalid.[1] Consequently, to avoid summary judgment, Defendants must adduce sufficient evidence to demonstrate that they can meet that burden. As the Federal Circuit stated in the context of a motion for summary judgment to dismiss an invalidity defense: "The moving party need not produce evidence showing the absence of a genuine issue of material fact; rather, the burden on the moving party may be discharged by… pointing out to the district court that there is an absence of evidence to support the nonmoving

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[1] *See Schumer v. Lab. Computer Sys., Inc.*, 308 F.3d 1304, 1315 (Fed. Cir. 2002); *Forest Labs., Inc. v. Ivax Pharms, Inc.*, 438 F. Supp. 2d 479, 486 (D. Del. 2006) (challenger must establish "by clear and convincing evidence that the [prior art] reference contains each and every limitation of the claimed invention"); *LP Matthews, LLC v. Bath & Body Works, Inc.*, 2006 US Dist LEXIS 76114 at 13 (D. Del. Oct. 19, 2006) ("Issued patents are presumed valid, and the underlying determination of invalidity must be predicated on facts established by clear and convincing evidence.") (quoting *Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1362 (Fed. Cir. 1998) (internal quotations omitted)).

party's case." *Avia Group Int'l. v. L.A. Gear California, Inc.*, 853 F.2d 1557, 1560 (Fed. Cir. 1998) (citing *Celotex Corp. v. Catrett*, 477 U.S. 317, 323-24 (1986) (internal quotations omitted); *see also Intel Corp. v. Broadcom Corp.*, 173 F.Supp.2d 201, 206 (D. Del. 2001).

For this reason, Defendants repeated reliance on a purported "battle of the experts" (Defs.' Opp. at 8) is simply unavailing. The law is clear that a party cannot fend off summary judgment simply by hiring experts to disagree with the movant's assertions. *See Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1278 (Fed. Cir. 2004) (expert opinions "reached using words in ways that contradict their plain meaning" do not create a material factual dispute for trial); *Arthur A. Collins, Inc. v. N. Telecom Ltd.*, 216 F.3d 1042, 1046 (Fed. Cir. 2000) ("a party may not avoid summary judgment simply by offering an opinion of an expert" about infringement; courts must scrutinize factual foundation of opinions); *Zelinski v. Brunswick Corp.*, 185 F.3d 1311, 1317 (Fed. Cir. 1999) (conclusions of expert that are not well-grounded in facts do not raise a genuine issue of material fact to defeat summary judgment); *see also Mid-State Fertilizer Co. v. Exchange Nat'l Bank of Chicago,* 877 F.2d 1333, 1339 (7th Cir. 1989) ("an expert's declaration, full of assertion but empty of facts and reasons, won't get a case past a motion for summary judgment, for the judge must look behind [the expert's] ultimate conclusion ... and analyze the adequacy of its foundation") (citation omitted)). Indeed, were that not the case, no court could ever grant summary judgment (concerning anticipation or virtually any other issue) in the face of an expert opinion, however deficient, that repeats the non-movant's contentions.

Because Defendants bear the burden of proving invalidity by clear and convincing evidence, they must do more than simply assert a battle of the experts – they must adduce evidence sufficient to show that they can meet their burden at trial. Defendants do not (and

cannot) dispute the actual contents of the purportedly anticipating Bhasker reference, and they cannot preclude summary judgment simply by asserting that their experts disagree with Plaintiffs' over the disclosure of the reference. To the contrary, if the Court finds, as Plaintiffs have shown, that the evidence presented by Defendants is of insufficient "quantum and quality" to allow a rational finder of fact to find anticipation by clear and convincing evidence, summary judgment of no anticipation is warranted. *See Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 254 (1986); *accord Avia*, 853 F.2d at 1560 ("If the evidence of the nonmovant is merely colorable, or is not significantly probative, summary judgment may be granted." quoting *Anderson*, 477 U.S. at 249-50)).

B. Bhasker, Which Expressly Describes Progressive Dementias As Untreatable, Cannot Anticipate The Claimed Method Of Treating Alzheimer's Disease.

Defendants cannot dispute what Bhasker actually says about progressive dementia (which Defendants argue includes Alzheimer Disease) – namely that, "with regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible." Ex. 2, Bhasker at 45, ¶ 5. Defendants attempt to escape this plain language by transmuting the term "treatment" into "cure" and "management" into "treatment." (Defs' Opp. at 11-13) This semantic ploy cannot transform Bhasker into a reference that clearly and convincingly anticipates the asserted claims of the '318 Patent. A reference that teaches progressive dementia as untreatable cannot constitute written description of a treatment for Alzheimer's disease.

Dr. Davis's patent claims a method of treating Alzheimer's disease that will "improve the cognitive function of patients with Alzheimer's disease." Ex. 1, '318 Patent 1:41-42. Both parties agree that this requires improving or alleviating the cognitive impairment associated with Alzheimer's disease. *See* Defendants' Opening Brief on Claim Construction at 11; Plaintiffs' Opening Brief on Claim Construction at 11. Nothing in Bhasker even suggests –

let alone clearly and convincingly teaches – any method to achieve this result. From start to finish, Bhasker disavows this objective in cases of "progressive dementia," and offers hope only in a wholly different form of dementia, which Bhasker refers to as "reversible dementias" – a category, which it clearly distinguishes from progressive dementia.

Bhasker begins with the proposition that "corrective treatment is usually, therefore, one associated with a gloomy outlook because a dementing process in most cases is relentlessly [a] progressive one." Ex. 2, Bhasker at 45, ¶ 1. It then identifies two situations where "this gloomy picture" is either "thoroughly wiped out" or "can be arrested or reversed to a minor extent": (1) where there is either "a metabolic or endocrinal deficit," or (2) where there are "tumours which may be removable or infections that can be successfully arrested, post-traumatic dementias, and low pressure hydrocephalus." *Id.* at ¶¶ 2, 3. Bhasker then distinguishes such cases from "irreversible cases," which it describes as "the category of dementias where there is a progressive fall-out of neurons when the course of the illness is rapidly downhill." *Id.* at ¶ 4. It is this category of "progressive dementias" as described by Bhasker that Defendants assert includes Alzheimer's disease. (Defs.' Opp. at 9.)

However, Bhasker emphasizes the importance of distinguishing the treatable from untreatable dementias through diagnosis and plainly states that, in this regard, the progressive dementias are untreatable. Specifically, the Bhasker reference states that "the compartmentalization into treatable and untreatable dementias has to be made with the utmost care" and that "[w]ith regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible." *Id.* at ¶¶ 4-5. It is impossible to read Bhasker's description of progressive dementia as holding any hope for improving cognitive function of patients with Alzheimer's disease, as described and claimed in the '318 Patent.

Bhasker's *only* discussion of drugs that would improve cognitive function is in its reference to Dr. Luria and "suggested measures of improving the higher functions in cases of local brain damage, like tumour, head injury, infarct, etc." via daily doses of cholinesterase inhibitors, including galantamine. Ex. 2, Bhasker at 46, ¶ 4. However, these cases all fall within the category of "treatable" dementias of the type that Bhasker describes in paragraphs 2 and 3 of the previous page, which it urges must be distinguished from "untreatable" progressive dementia "with utmost care." Obviously, this part of Bhasker does NOT disclose the method, claimed in the patent, for "improv[ing] the cognitive function of patients with Alzheimer's disease." Ex. 1, '318 Patent at 1:41-42.

REDACTED

The same is true of the other parts of Bhasker's article. Bhasker devotes three paragraphs (Ex. 2 at 46, ¶¶ 1-3) to such matters as the "control of convulsions and involuntary movements," stressing "the importance of controlling these *associated disorders which may sometimes assume greater importance than the dementia itself*" (emphasis added). The only drug that it discusses in this context is "Haloperidol," which is "very useful . . . in the control of hyperkinetic dyskinesias." *Id.* at ¶ 1. Such a drug is used for an "associated disorder," and is never described as a drug to improve cognitive functions. Another paragraph (*Id.* at 46, ¶ 2) is devoted to the "profound behavioral problems met with in patients with dementia." Another describes the "careful supervision and devoted nursing care" that is necessary for a demented person. *Id.* at ¶ 3. Bhasker also refers to the "social aspects [of dementia] such as adequate counseling and marriage." *Id.* at ¶ 5. Finally, it concludes that "[t]he problem of managing a demented individual in [sic is] a very real one needing adequate judgment, judicious use of drugs, sympathetic nursing, and proper counseling" (*Id.* at 47). The "judicious use of drugs" to

which Bhasker refers can only sensibly mean drugs like Haloperidol – which can "control" symptoms associated with progressive dementia like hyperkinetic dyskinesias. None of these passages in Bhasker so much as hint at a treatment for Alzheimer's disease (or its core symptom of cognitive impairment) using drugs.. **REDACTED**

Nothing in the expert report of Defendants' expert, Dr. Levey, can compensate for Bhasker's failure to discuss any treatment of Alzheimer's disease that could improve the cognitive function of patients.

REDACTED

The fact remains that the Bhasker reference describes neither curative nor symptomatic treatment for progressive dementia.

This absence from Bhasker is further emphasized by comparison to the discussion, occurring in the very next paragraph (Bhasker at 46, ¶ 1), concerning treatment of the movement disorders of Huntington's Chorea. In that case, **REDACTED**

Bhasker does describe a symptomatic treatment (there, Haloperidol for the choreic movements of the disease). **REDACTED** Hence, Bhasker's explicit reference to treating certain symptoms of Huntington's Chorea, immediately following its express statement that no treatment was possible for progressive dementias, makes plain both that Bhasker's consideration of treatments includes possible symptomatic ones and, hence, that its statement that no treatment is possible for progressive dementia rules out both curative and symptomatic treatments.[2]

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[2] Indeed, the Bhasker reference also takes pains to makes clear that, in the case of Huntington's Chorea, what is being treated is not the dementia, but the "associated disorders (continued...)

Plaintiffs have shown in Section A above that Defendants must point to evidence that raises a material issue of fact that could support the conclusion that it is "clear and convincing" that Bhasker disclosed all of the elements of the asserted claims of the '318 Patent. Defendants' semantic argument and Dr. Levey's expert report do not show that a reasonable fact-finder could find anticipation even under a predominance of the evidence standard, let alone the clear and convincing standard that applies here.

C. Defendants' Reliance On Purported Knowledge Of A Skilled Artisan Cannot Cure The Deficiencies In Bhasker.

Defendants' Opposition hinges on a distorted view of the doctrine of anticipation. Defendants erroneously claim that elements missing from a prior art reference may be supplied by the knowledge of one skilled in the art. At issue is what one with ordinary skill in the art would understand as the subject matter disclosed, not what one with ordinary skill in the art may assemble from the prior art in combination with additional information from beyond the four corners of the reference as Defendants do.

The indisputable fact remains that the Bhasker reference mentions galantamine only once, in the last full paragraph of page 46, in the context of discussing "measures of improving the higher functions *in cases of local brain damage like tumour, head injury, infarct etc.*, by deinhibitory procedures and re-education of the rest of the brain." Ex. 2, Bhasker at 46, ¶ 4. It is conceded that "local brain damage" does not include Alzheimer's disease. Instead, to connect galantamine to Alzheimer's disease, Defendants' combine this discussion of "deinhibitory procedures" with additional knowledge, attributed to one of ordinary skill,

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which may sometimes assume greater importance than the dementia itself." Ex. 2, Bhasker at 46, ¶ 1. Hence, even in the context of treating Huntington's Chorea, Bhasker makes clear that no treatment (including symptomatic treatment) is possible for the dementia.

concerning the characteristics of both Alzheimer's disease and galantamine, none of which is even hinted at in Bhasker itself. Defendants' argument is wholly at odds with the settled law of anticipation.

Express anticipation requires direct and distinct description of all claim features with nothing being left to implication or inference. *See Jamesbury Corp. v. Litton Indus. Prods.*, 756 F.2d 1556 (Fed. Cir. 1985), *overruled on other grounds*; *Structural Rubber Prod. Co. v. Park Rubber Co.*, 749 F.2d 707 (Fed. Cir. 1984). Defendants concede, as they must, that express anticipation is not present here, since (among other things), Bhasker makes no mention of Alzheimer's disease. Defendants instead attempt to rely upon the doctrine of inherent anticipation, but this requires Defendants to demonstrate that the descriptive matter missing from the express description in the reference is nonetheless *necessarily* present inherently, and that it would be so recognized by one of ordinary skill in the art. *See Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed Cir.1991); *LP Matthews*, 2006 US Dist. Lexis 76114 at 11 ("an inherent limitation is one that is necessarily present and not one that may be established by probabilities or possibilities"); *Rockwell Int'l. Corp. v. SDL, Inc.*, 103 F. Supp. 2d 1202, 1207 (N.D. Cal. 2000) ("An absent element is inherently disclosed only if a skilled artisan would recognize that the element is necessarily practiced by the reference.") *Structural Rubber*, 749 F.2d at 716 ("While the teaching in the prior reference need not be *ipsissimis verbis*, nevertheless, there must be a teaching with respect to the entirety of the claimed invention."). Importantly, and fatally to Defendants' anticipation attack, Defendants cannot use the doctrine of inherent anticipation to fill gaps or expand the disclosure in a reference; instead, it serves the much more limited role of explaining to a lay reader those elements of a reference which a skilled artisan would recognize as present. *See Scripps Clinic & Research Found. v. Genentech,*

Inc., 927 F.2d 1565, 1576-77 (Fed. Cir. 1991) ("The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, *not to fill gaps in the reference*") (emphasis added); *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991) ("Extrinsic evidence may be considered when it is used to explain, *but not expand*, the meaning of a reference.") (emphasis added).

Thus, while the doctrine of inherent anticipation allows for examination of the implicit disclosures of a prior art reference – i.e., that which exists in the prior art reference but which is not expressly disclosed – it "does not grant a license to read into the prior art reference teachings that are not there." *See Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473 (Fed. Cir. 1997). Anticipation always requires that all of the elements of a patent claim exist in a single prior art reference; this rule does not change when the doctrine of inherency is used. The assertedly inherent elements must *necessarily* be present, and cannot be found present merely on the opinion of Defendants' experts. *See Finnigan Corp. v. Int'l Trade Comm'n.*, 180 F.3d 1354, 1365 (Fed. Cir. 1999) (expert testimony that one skilled in the art may see missing element as present held insufficient for inherency). "An expert's conclusory testimony, unsupported by the documentary evidence, cannot supplant the requirement of anticipatory disclosure in the prior art reference itself." *Motorola,* 121 F.3d at 1473.

Defendants do not (and cannot) show that Bhasker expressly discloses all of the elements of the asserted claims of the '318 Patent. In particular, Bhasker indisputably does not expressly describe Alzheimer's disease, let alone the use of galantamine as a treatment for Alzheimer's disease. The single reference to galantamine in Bhasker comes in the context of reporting Dr. Luria's work in treating "local brain damage,"

REDACTED

To try to overcome this deficiency in the reference, Defendants repeatedly rely – in the guise of inherency – upon what they assert would be the knowledge of one of ordinary skill in the art. Specifically, in order to connect Bhasker's single reference to galantamine in the context of local brain damage to the claimed invention of using galantamine to alleviate the cognitive decline in Alzheimer's disease, Defendants assert the following additional pieces of information, purportedly available to one of ordinary skill in the art: (1) that Alzheimer's disease is characterized by a central cholinergic deficit, and (2) that galantamine crosses the blood-brain barrier so as to get into the brain. Defs.' Opp. at 16. These concepts, however, are plainly absent from the Bhasker reference itself. That is, the additional information Defendants seek to use in their anticipation challenge are not "inherent" in Bhasker, but instead is wholly separate knowledge, gained from entirely different references.

REDACTED

Similarly, Bhasker contains no discussion of galantamine's pharmacology and indeed references that drug interchangeably with neostigmine, a different drug which does not cross the blood-brain barrier and does not treat Alzheimer's disease.

REDACTED

Plainly, Defendants' anticipation argument goes beyond merely explaining what is in Bhasker and

instead baldly extends to filling gaps and expanding the teachings of that limited, two-page document. Such "inspired recourse to the existing literature" cannot support an anticipation defense. *See Biogen, Inc. v. Amgen, Inc,*. 973 F. Supp. 39, 45 (D. Mass 1997).

In *Structural Rubber,* the Federal Circuit rejected the very contention that Defendants advance here. *See* 749 F.2d at 716. In that action, the validity of two patents directed to highway railroad crossings was challenged based upon, among other things, alleged anticipation over prior art. *Id.* at 714-15. The challenger admitted that the prior art did not disclose every element of the patents in suit, but argued that for anticipation purposes, "missing elements may be supplied by the knowledge of one skilled in the art or the disclosure of another reference." *Id.* at 716. In refuting the challenger's position, the court explained that although a prior art disclosure that "almost" meets the standard for anticipation may render a claim invalid due to obviousness, such an incomplete disclosure cannot anticipate. *Id.* (stating whether "one of ordinary skill may in reliance on the prior art complete the work required for the invention .... relate[s] to obviousness, not anticipation").

In *Forest Laboratories*, this Court (per Judge Farnan) followed *Structural Rubber* and rejected the accused infringer's attempt to read into a prior art reference the knowledge of a skilled artisan concerning stereo isomers. *See* 438 F. Supp. 2d at 486. Instead, the absence of teachings in the reference itself doomed the defense. *See Id.* Similarly, the *Rockwell* Court rejected an effort to enhance an allegedly anticipating reference with the knowledge of one skilled in the art, observing that "the question of whether one of ordinary skill may in reliance on the prior art complete the work required for the invention relates to obviousness, not anticipation." 103 F.Supp.2d at 1206 (quoting *Structural Rubber*, 749 F.2d at 716 (emendations in original)). The *Rockwell* Court was unambiguous on this point: "[T]he common knowledge

of a skilled artisan cannot be used to add an inherent element into a patent claim for the purpose of a section 102 anticipation analysis." *Id.* at 1207.

Defendants' attempt to read into Bhasker teachings that it plainly does not contain and that are only supplied from knowledge of other references is contrary to established law and insufficient to raise material issues of fact that could clearly and convincingly establish anticipation.

D. Defendants Cannot Preserve Their Baseless Anticipation Challenge By Asserting Obviousness.

As a last ditch effort, Defendants assert that "even if the Court were to find that there are no genuine issues of material fact" summary judgment should be denied because Defendants have also asserted Bhasker as part of their obviousness challenge. (Defs.' Opp. at 1, 17.) But Defendants' assertion of an obviousness attack provides no warrant for maintaining a baseless anticipation challenge as well. To the contrary, as Defendants' argument makes transparent, their simultaneous assertion of an obviousness attack based on Bhasker raises the specter of conflating the two challenges and thereby improperly circumventing the important substantive limitations on an obviousness defense.

As the Federal Circuit explained in *Duro-Last, Inc. v. Custom Seal, Inc.*, "obviousness and anticipation are related, but are legally distinct and separate challenges to a patent's validity [and]... require different elements of proof." *Duro-Last, Inc.*, 321 F.3d 1098, 1107-08 (Fed. Cir. 2003); *see also Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984) (noting that it is improper to confuse anticipation with obviousness). The core of Plaintiffs' argument against anticipation is that the '318 Patent (and not Bhasker) contains the first disclosure of Dr. Davis's invention of using galantamine to treat Alzheimer's disease. Nevertheless, it is clear that Defendants wish to preserve their anticipation defense to muddy the inquiry into obviousness

because the objective considerations of non-obviousness weigh so heavily against them.[3] Defendants should not be permitted to mount – and Plaintiffs should not be subjected to – a baseless anticipation defense to shore up the serious deficiencies of Defendants' obviousness attack.

CONCLUSION

For the foregoing reasons, this Court should grant Plaintiffs' Motion and dismiss Defendants' defenses and related counterclaims based on anticipation under 35 U.S.C. § 102.

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[3] For example, the record demonstrates considerable skepticism and numerous failures by others attempting to develop a method of treating the symptoms associated with Alzheimer's disease – factors that weigh heavily against Defendants' obviousness case. Defendants have made clear they wish to preserve their anticipation challenge in order to avoid an inquiry into the objective considerations of non-obviousness. (Defs.' Opp. at 13 n. 10)

EXHIBIT 1

United States Patent [19]
Davis

[11] **Patent Number: 4,663,318**
[45] **Date of Patent: May 5, 1987**

[54] **METHOD OF TREATING ALZHEIMER'S DISEASE**

[76] Inventor: **Bonnie Davis**, 17 Seacrest Dr., Huntington, N.Y. 11743

[21] Appl. No.: **819,141**

[22] Filed: **Jan. 15, 1986**

[51] Int. Cl.[4] A61K 31/55
[52] U.S. Cl. 514/215
[58] Field of Search 514/215

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[57] **ABSTRACT**

Alzheimer's disease may be treated with galanthamine.

7 Claims, No Drawings

METHOD OF TREATING ALZHEIMER'S DISEASE

GENERAL FIELD OF THE INVENTION

The present invention relates to a novel method of treating Alzheimer's disease and more particularly to a treatment using galanthamine.

BACKGROUND ART

Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in Anaesthesia 29 163–8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in Acta Anesth. Scand. 24:166–168 (1980) describe the effect of galanthamine on plasma ACTH values during anaethesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.

Il'yuchenok et al (Chemical Abstracts 70 36296K describe the appearance of θ-rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.

Increase in short-term memory in dogs by use of galanthamine is described by Krauz in Chemical Abstracts 81 72615Z.

The antagonistic effect of galanthamine to scopolamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157Z, and in Zhurnal Vysshei Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA) 26:1091-1093, 1976.

Alzheimer's disease, presenile dementia, causes much distress not only to those suffering from the disease, but also those who are close to them. The custodial care of advanced victims of the disease is a tremendous expense to society. At present, there is no effective means of improving the functional status of persons with the disease.

It is an object of the present invention to improve the cognitive function of patients with Alzheimer's disease.

SUMMARY OF THE INVENTION

A method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof. A radioactively-labelled form of the molecule may also serve as a diagnostic test for Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

Galanthamine can be administered in any convenient chemical or physcial form. For example, it may be administered as its hydrobromide, hydrochloride, methylsulfate or methiodide.

Galanthamine or its pharmaceutically-acceptable acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous, injection, or intracerebroventricularly by means of an implanted reservoir. It may be necessary to begin at lower doses than are ultimately effective.

Galanthamine and its acid addition salts form crystals. They are in general only sparingly soluble in water

at room temperature and so injectible compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1–50 mg/ml more commonly 5–40 mg/ml, for example, 5–30 mg/ml or 10–40 mg/ml, typically 20–30 mg/ml of galanthamine. Typical dosage rates when administering galanthamine by injection are in the range 5–1,000 mg per day depending upon the patient. For example, divided doses in the range 0.5–5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50–300 mg per day to a patient of a body weight of 40–100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

Galanthamine or its pharmaceutically-acceptable acid addition salts may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100–600 mg per day. In preparing such tablets or capsules, standard tablet or capsulemaking techniques may be employed. The dosage rate of galanthamine or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing galanthamine tablets. Capsules may be prepared using soft galatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine which release the contents over a period of several hours thereby maintaining a constant level of galanthamine in the patient's blood stream.

The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacyin Alzheimer's disease. Haroutunian, V, Kanof P, Davis, K.L: Pharmacological alleviations of cholinergic-lesion-induced memory defects in rats. Life Sciences 37:945–952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg galanthamine hydrobromide to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5 mg/5 ml and 25 mg/5 ml concentration.

There have been reports that galanthamine can cause cardiac arrythmias. In such cases, it may be desirable to

administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrythmias.

I claim:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5–1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50–300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10–2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100–600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

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EXHIBIT 2

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MEDICAL MANAGEMENT OF DEMENTIA*

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DEMENTIA is neither a disease *per se* nor a single symptom. It may be considered to be a clinical manifestation resulting from complex structural or functional changes in the most sophisticated mechanisms of the brain. The corrective treatment is usually therefore, one associated with a gloomy outlook, because a dementing process in most cases is a relentlessly progressive one, and very often not amenable even to diagnosis.

On the other hand, this gloomy picture is thoroughly wiped out and a favourable result readily obtained when one of the treatable underlying causes is detected; the prognosis becomes 'excellent' when the correctable cause is diagnosed early and found to be a metabolic or endocrine deficit (as in Pellagra, B_{12} deficiency or Myxœdema). In such cases, the dementia can be cleared up and the patient can have a complete "cure".

On the other hand, the dementing process can be arrested or reversed to a minor extent in some instances, where only a guarded prognosis can be offered. These situations include the cases of tumours (when removable), infections (like GPI) when they can be "successfully" arrested, post-traumatic dementias, and low pressure hydrocephalus.

The irreversible cases belong to the category of dementias where there is a progressive fall-out of neurons and the course of the illness is rapidly downhill. Therefore, the importance of a thorough diagnosis even at the first instance must be realised, because the compartmentalisation into treatable and untreatable dementias has to be made with the utmost care. Moreover it must be emphasised that in certain situations (like Myxœdema) a *late* diagnosis of the underlying cause may lead to irreversibility of the mental status, especially so, in the young developing brains.

With regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible. The problem of who is going to manage the dementing individual arises next. Contrary to the older beliefs that the demented person (who is likely to be insane) has to be necessarily managed by a psychiatrist or an internist, it now appears that the Neurologist is the best person to handle them, and a neuropsychiatrist is the ideal person. The neurologist remains today at the centre of a triangle formed by the psychiatrist, the general physician and the neurosurgeon[1].

*Summarised from the talk given at the Institute of Neurology.
Specially contributed to the 'ARYAVAIDYAN'.

The control of convulsions and involuntary movements are separate subjects by themselves. But what must be stressed is the importance of controlling these associated disorders which may sometimes assume greater importance than the dementia itself. For example, in cases of Huntington's chorea where the dementia may be very slowly progressive, the involuntary movements may present the main problem, when adequate control of the choreic movements enables the individual to go back to his work. Rewarding experiences are on record of having treated patients with Huntington's Chorea by giving Haloperidol, a very useful drug in the control of hyperkinetic dyskinesias.

The behavioural problems met with in patients with dementia are profound and so depending upon the nature of the behavioural disturbance, judicious use may be made of drugs, along with psychiatric care. General surgical therapy does not find a significant role in dealing with patients suffering from progressive dementia except when there is an isolated behavioural aberration that can be selectively tackled by Stereotaxy. Even then, any beneficial response is short-lived and soon overtaken by the dementing process.

A demented person obviously requires careful supervision and devoted nursing care as he will not be able by himself to attend to his own nutrition and personal cleanliness; he is also likely to be unmindful of any intercurrent illnesses that may supervene.

The restoration of higher cortical functions is difficult and was once considered to impossible; but it has lately gained importance. Luria and his colleagues have dealt with this problem in great detail. They have suggested measures of improving the higher functions in cases of local brain damage like tumour, head injury, infarct etc, by deinhibitory procedures and re-education of the rest of the brain. Deinhibition refers to the facilitation of acetylcholine activity by giving small daily doses of Cholinesterase inhibitors (Neostigmine, Gallanthamine etc.). Empirical measures, like trying anabolic steroids, vasodilators, nucleic acid preparations, amines and aminoacids are in vogue, but have not been of any great value. The problem of sending a demented individual back to his profession has to be adequately studied by the attending physician before coming to a definite decision. If he happens to hold a position requiring the use of proper judgement, it is better that he is relieved of such a responsible post and assigned a less exacting, general type of work.

The social aspects include adequate counselling in marriage affairs when a demented person or a relative of a demented

person seeks advice. The stigma associated with dementia is equal to that with epilepsy. This fact must be kept in mind by the physician, when confronted with a case of dementia and especially the relatives.

The problem of managing a demented individual in a very real one needing adequate judgement, judicious use of drugs, sympathetic nursing and proper counselling.

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DEATHS INVOLVING PROPOXYPHENE

A STUDY OF 41 CASES OVER A TWO-YEAR PERIOD

Forty-one deaths occurred involving propoxyphene hydrochloride (Darvon) during a two year period. Ten patients died from propoxyphene intoxication alone, while 12 were victims of a propoxyphene alcohol combination, the latter number being identical to the deaths from a combination of barbiturates with alcohol seen during the same period. Five young women died from an ingestion of propoxyphene following an argument. Four patients could be categorized as drug abusers due to historical circumstances. The high levels of propoxyphene suggested habituation in three instances. Physicians should be alerted to the potential deleterious effects of indiscriminate use and abuse of propoxyphene, and should warn their patients not to drink alcoholic beverages when taking propoxyphene. They should use extreme caution when prescribing it to those in the younger age-group.

An impressive factor in this series is the availability of the drug to young people who, after a sudden argument, seem to find ingestion of pills a convenient gesture at attempted self-destruction. There were five cases of teenagers (all girls) in this series (aged 15 to 20 years) whose deaths were caused by propoxyphene intoxication, and in none of these were alcohol, other drugs or narcotics addiction involved. In two instances, the victims were found to be pregnant. Ten of the 22 patients who died from ingestion of propoxyphene alone, or propoxyphene in combination with alcohol, were over 40 years of age. while two of the deaths due to the combination were in patients over 60 years of age.

Concerning the manner of death, 17 of the 41 cases were classified as suicide, with six of these solely from the ingestion of propoxyphene.

Eighteen of the 41 patients received a prescription of propoxyphene from one or more private physicians. Seven of these patients eventually died from ingestion of propoxyphene or propoxyphene with alcohol. In 12 instances, the patient secured a prescription as an outpatient from a clinic. —(Sturner Q. William and Garriott C. James, *J.A.M.A.*, 5-3-1973).

EXHIBIT 3

REDACTED

EXHIBIT 4

REDACTED

EXHIBIT 5

REDACTED